that is changing with respect to public attitudes toward medicine and the other professions, and these changes can be for better or for worse. They need to be understood, and influenced for the better where this is possible. And above all there is a need to show the public that the profession cares—cares about costs, cares about health and cares about people. We do a great deal of all of this now, but we could and should do more. We can do a lot more to help dissipate the health care smoke screens, and this would surely be good politics as well.

—MSMW

Interpreting Steroid Receptor Assays

THERE IS LITTLE QUESTION that estrogen and progesterone receptor determinations can substantially increase the accuracy of treatment regimens for patients with advanced breast cancer. However, noncritical acceptance of (and therapeutic decisions) based on findings from a single laboratory test may often result in disappointment; steroid receptor analyses on human breast tumors are no exception. In order to achieve maximal predictive accuracy, test results must be carefully interpreted in the biologic setting in which they have relevance. For this reason, it is of extreme value for clinicians to consider sources of noise in these assays; that is, explanations for observed responses to endocrine therapy in patients considered estrogen receptor (ER) negative and failure to obtain endocrine responses in patients termed ER positive.

The most common explanation for a so-called *false negative* result (tumor ER negative but patient responds to endocrine therapy) is laboratory error. Steroid receptors tend to be fragile proteins whose binding activity is pH and ionic strength dependent; in addition, they are thermolabile. Any number of errors in sample storage, handling or assay technique will convert an ER positive tumor to an apparently negative one. In a recent survey of approximately 65 laboratories doing ER assays, about a fourth of those responding incorrectly assessed ER concentrations in one or more of four standardized samples. (More than a third of laboratories failed to satisfactorily assess at least one of four samples for progesterone receptor.)

Most assays are made on cytoplasmic extracts. Previous exposure to endogenous hormone may have already caused receptor occupancy and subsequent nuclear translocation. In fact, recent data have suggested that in about 5 percent of tumors, receptor may be localized to the nucleus even in the absence of endogenous hormone. In either case a receptor containing tumor will be missed.

Heterogeneity of receptor content may exist at the microscopic or macroscopic level. That is, a tumor metastasis may be largely composed of non-receptor containing abnormal elements which dilute the receptor present in a few tumor cells. Alternatively, a biopsy specimen from a metastatic lesion may be ER negative while remaining sites in which response is assessed are ER positive. Inadvertently, a specimen submitted for ER assay may be either necrotic or adjacent to the actual tumor containing tissue. Falsely negative test results ensue.

Finally, a given endocrine therapy may be mediated via another receptor. For example, if an occasional patient with breast cancer responds to hypophysectomy because of a reduction in prolactin levels, and if expression of prolactin receptors were imperfectly linked to ER, then some ER negative tumors might respond to pituitary ablation.

While the overall response to endocrine therapy in ER negative patients is low (less than 10 percent in all major series) it is not zero, and these data point up the fact that no single laboratory test ought to be used to proscribe endocrine therapy forever in a given patient.

Far more frequently, patients are thought to have ER positive tumors but objective responses to endocrine therapy fail to materialize. A proper understanding of the setting in which this may occur can substantially improve the likelihood of success. First, so-called *false positive* results can arise through a variety of methodologic errors. It is unfortunately all too simple for poorly chosen assay techniques to fail to distinguish progesterone receptor from glucocorticoid receptor or corticosteroid binding globulin, and androgen or estrogen receptor from sex steroid binding globulin. Also, heterogeneity of cells within or between metastatic lesions with respect to binding activity may yield false positive results. That is, a tumor may contain sufficient ER to give a positive result but most of the cells may be ER negative and unresponsive. Alternatively, the assessed tumor nodule may be ER positive and hormone responsive but

different binding properties of other tumor sites result in a mixed or negative response to endocrine therapy. With respect to the former case (heterogeneity within tumors) one might expect there to be a positive relationship between concentration of ER and likelihood of endocrine response and this has been shown to be true in many series. Therefore, the predictive value of the test is considerably improved by quantitative assessment of ER concentrations.

There are many steps in steroid hormone action distal to the initial binding of the hormone to the receptor. Obviously, a defect in any one of these would result in an unresponsive tumor with apparently normal binding activity. An obvious solution to this problem is some assessment of the tumor response mechanism *in toto*. Elsewhere in this issue, Osborne and McGuire review the usefulness of the estrogen induced protein progesterone receptor in this regard.

It is illogical to expect that ER concentrations ought to predict response to a host of endocrine therapies, many of which (androgen or progestin administration, for example) may not be directly mediated by ER. Consequently, if a tumor lacks the receptor required for that therapy but contains ER a false positive result will be observed.

Finally, a tumor may in fact be hormone responsive, but the chosen therapy inadequate. For example, it is correct that responses to adrenalectomy are less frequent in patients who have not responded to oophorectomy; nonetheless, 10 percent to 15 percent of these patients will have objective responses to adrenalectomy. The latter therapy proves that these patients have hormone dependent tumors, but if they are assessed on the basis of the oophorectomy (which presumably was not able to sufficiently alter the hormonal milieu) the findings would not have been *false positive.*

Clearly, by knowing the site that was used for the ER assay, by being certain that the sample was transported and stored correctly, and by learning whether the assay methodology employed is valid, clinicians can vastly increase the odds in favor of getting helpful information. Given the cost of the assay, the necessity of a biopsy study and the amplified hazards of an incorrectly chosen therapy, it is highly appropriate for clinicians to demand that the assay laboratory prove the reliability of the assay by showing appropriate correlations with endocrine therapy in previous tests and by accurate results on unknown standards which are now available. With the large number of laboratories offering tests of dubious quality a caveat emptor attitude is surely warranted.

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Organized Medicine as 'My Doctors'

THERE ARE MILLIONS of people in this nation who have great confidence in the knowledge, integrity and skills of their own doctors but who are less sure of the integrity and skills of other people's doctors or of the medical profession as a whole. It is usually other people's doctors, and not "my doctor," who are perceived to be responsible for all the bad things they hear about doctors. Unfortunately organized medicine has become identified in the public consciousness more with other people's doctors than with "my doctors." Yet it is obvious that the medical profession is just as much made up of "my doctors" as it is of other people's doctors.

It would seem that the key is to be found in the doctor-patient relationship. The strength of a patient's confidence and trust in a physician seems to be more or less proportional to the strength of this relationship, but so far it has not been possible to project this to the relationship between the medical profession or organized medicine and the public or society as a whole. The fact is that medicine has been losing some ground in recent polls of public trust and esteem, although the profession still ranks relatively high and certainly above many if not most of its detractors. But the trend is negative and it should behoove the profession to begin to reverse it as quickly as possible.

It is suggested that the profession and organized medicine should try somehow to make the doctor-patient relationship come alive in the broader relationship between medicine and American society. A way to do this might be for physicians and organized medicine to become as visibly concerned with the health, quality of life and personal fulfillment of the individual person in today's society just as "my doctor" is concerned with